Remarks

Claims 1-9, 12-18, 21-25, 28-30 and 33-37 are pending in this application. No claim amendments are made in this paper. Applicants respectfully submit that all pending claims are allowable for the following reasons.

A. The Rejection Under 35 U.S.C. § 103(a) Should Be Withdrawn

On pages 2-5 of the Office Action, the rejection of claims 1-9, 12-18, 21-25, 28-30 and 33-37 under 35 U.S.C. § 103(a) is maintained as allegedly obvious over U.S. Patent No. 5,830,500 to El-Rashidy *et al.* ("the '500 patent") in view of U.S. Patent No. 5,104,899 to Young et al. ("the '899 patent") and WO 97/28788 ("the '788 publication"). In particular, it has been alleged in previous office actions that the pending claims are obvious because: 1) the '500 patent discloses a lactose-free composition of fluoxetine and the '899 patent discloses compositions of (S)-fluoxetine; 2) the '500 patent discloses fluoxetine compositions made from dry ingredients; and 3) dissolution time is an art-recognized result-effective variable as evidenced by the '788 publication. Applicants respectfully disagree with each of these allegations for the following reasons.

In Applicants' response to previous office action, Applicants stated that there is no suggestion in the '500 patent that lactose should be avoided in the fluoxetine compositions. In response, the Examiner alleges that such suggestion is not necessary because the '500 patent discloses a lactose-free fluoxetine composition, thereby suggesting to one of ordinary skill in the art that lactose-free fluoxetine compositions are "useful and effective." Office Action, page 4. Applicants respectfully disagree.

As the Examiner is aware, one of the criteria that must be satisfied to establish a *prima facie* case of obviousness is that there must be some suggestion or motivation to modify or combine the cited references. Manual of Patent Examining Procedure ("MPEP"), § 2143. Applicants respectfully submit that although the '500 patent discloses a composition of racemic fluoxetine that does not contain lactose, no suggestion or motivation existed prior to this invention for those of ordinary skill in the art to combine the specific composition of the '500 patent with the compositions of (S)-fluoxetine disclosed in the '899 patent, which contain lactose. *See*, the '899 patent, col. 11, lines 1-46. Indeed, prior to this invention, those of ordinary skill in the art would not have had any reason to exclude lactose from pharmaceutical

formulations of racemic or optically pure fluoxetine, since lactose was "one of the most widely used direct-compression fillers" at that time. *See, e.g.*, Lieberman *et al.*, Pharmaceutical Dosage Forms: Tablets (Second Ed., Marcel Decker, Inc., 1989) ("Lieberman"), page 205, a copy of which is enclosed herewith. Therefore, contrary to the Examiner's allegation, the mere disclosure of a fluoxetine composition that does not contain lactose, without an express teaching that lactose-free compositions are preferable, would not have suggested to those of ordinary skill in the art the lactose-free compositions of this invention. Therefore, Applicants respectfully submit that the rejection of claims 1-9, 12, 29 and 33-34 should be withdrawn.

With regard to claims 21-25, 28-29 and 36-37, the Examiner alleges that the claims are obvious over the disclosure in the '500 patent of process wherein dry ingredients are mixed, because the term "anhydrous" as defined in this application does not exclude all water. In particular, the Examiner disagrees with Applicants' submission that the composition disclosed in the '500 patent cannot be anhydrous because it contains dicalcium phosphate dihydrate. In this regard, it is alleged that the water molecules in dicalcium phosphate dihydrate are "bound to the dicalcium phosphate and therefore would not be expected to detrimentally affect the overall composition." Office Action, page 4. Applicants respectfully disagree.

Applicants wish to draw the Examiner's attention to pages 204 and 213 of Lieberman, copies of which are also enclosed herewith. On page 204, Lieberman teaches that moisture content is among the considerations one must make in selecting a direct-compression filler. Specifically, Lieberman discloses that water of hydration of dicalphosphate (*i.e.*, dicalcium phosphate), among others, is a factor to be considered. Furthermore, on page 213, Lieberman teaches that dicalcium phosphate dihydrate will begin to lose water when exposed to temperatures of 40°C to 60°C. Most important, Lieberman teaches that when dicalcium phosphate dihydrate, is combined with a highly hygroscopic filler like microcrystalline cellulose, "the loss of moisture may be sufficient to cause a softening of the tablet matrix ... and to accelerate decomposition of moisture-sensitive drugs." Lieberman, page 213 (Emphasis added).

From Lieberman, it is clear that mere mixing of dry dicalcium phosphate dihydrate with other dry ingredients would not result in an anhydrous pharmaceutical composition. Moreover, the '500 patent expressly discloses the use of microcrystalline cellulose in a composition that contains dicalcium phosphate

dihydrate. The '500 patent, column 3, lines 37-40. In fact, the only fluoxetine composition disclosed in the '500 patent contains both dicalcium phosphate dihydrate and microcrystalline cellulose. *Id.*, column 4, lines 20-33. Because this combination is likely to yield a loss of moisture, Applicants respectfully submit that the '500 patent fails disclose or suggest an anhydrous fluoxetine composition, much less an anhydrous composition containing optically pure (S)-fluoxetine. Therefore, the rejection of claims 21-25, 28-29 and 36-37 should be withdrawn.

Claims 13-18 and 29-30 are rejected as allegedly obvious over the '500 patent in view of the '788 publication. In particular, it is alleged that although the '500 patent does not disclose the advantages of the dissolution time recited in the claims, the claims are obvious because the dissolution time of a tablet is an art-recognized result-effective variable as evidenced by the '788 publication. Office Action, page 5. Applicants respectfully traverse this rejection.

There must be some suggestion or motivation to modify or combine the cited references in order to establish a *prima facie* case of obviousness. MPEP, § 2143. As the Examiner correctly recognizes, the '500 patent does not disclose the advantages of the dissolution time recited in the claims. Office Action, page 5. In fact, by disclosing a formulation for "relatively rapid release of a drug," the '500 patent teaches away from a fluoxetine formulation having a dissolution time recited by the claims pending in this application. The '500 patent, Abstract and column 2, lines 12-17.

The '788 publication does not cure this deficiency. It is alleged that because the '788 publication discloses that "dissolution time is one of several known physical characteristics of a tablet, it would be obvious to one of ordinary skill in the art to further modify the fluoxetine compositions until a desired dissolution time ... is acquired." Office Action, page 5. Applicants respectfully point out that this statement does not provide a sufficient basis for a *prima facie* obviousness rejection. This is because the question relevant to the determination of *prima facie* obviousness is not whether those of ordinary skill in the art would have been able to make and use the (S)-fluoxetine composition with the recited dissolution time from the teachings of the cited references. Instead, the question is whether those of ordinary skill in the art would have been motivated to attempt to do so. Applicants respectfully submit that no such motivation existed prior to this invention since, as the Examiner recognizes, the '500 patent does not disclose the advantages of the dissolution time recited in the

claims. Therefore, Applicants respectfully submit that the rejection of claims 13-18 and 29-30 should also be withdrawn.

No fee is believed due for this submission. Should any fees be due for this submission or to avoid abandonment of the application, please charge such fees to Jones Day Deposit Account No. 503013.

Respectfully submitted,

Date April 5, 2004

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Enclosures

PHARMACEUTICAL DOSAGE FORMS

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Table 2 Factors Influencing Choice of Direct-Compression Fillers

1. Compressibility[a]
   a. Alone
   b. Dilution factor or capacity
   c. Effect of lubricants, glidants, disintegrants
   d. Effect of reworking
2. Flowability[a]
   a. Alone
   b. In the finished formulation
   c. Need for glidant
3. Particle Size[a] and Distribution
   a. Effect on flowability
   b. Effect on compressibility
   c. Effect on blending
   d. Dust problems
4. Moisture Content and Type[a]
   a. Water of hydration (lactose, dextrose, dicalphosphate)
   b. Bound and free moisture
   c. Availability for chemical degradation
   d. Effect on compressibility
   e. Hydroscopicity
5. Bulk Density[a]
   a. Compression ratio = $\frac{\text{volume of tablet}}{\text{bulk volume of powder}}$
   b. Effect of handling and blending
6. Compatibility with Active Ingredient
   a. Moisture
   b. pH
   c. Effect on assay
7. Solubility (in GI Tract)
   a. Rate of dissolution
   b. Effect of pH
8. Stability of Finished Tablets
   a. Color
   b. Volume
   c. Hardness
9. Physiological Inertness
   a. Toxicity
   b. Reducing sugar
   c. Osmotic effect
   d. Taste and mouth-feel (if appropriate)
10. Cost and Availability
11. Governmental Acceptability
    a. United States and foreign countries
    b. Master File
    C. GRAS status
    d. Compendial standards (N.F.)

[a]Need to set purchase specifications for each lot of raw material.

manufacturing uniformity is to be assured. This is particularly true in the case of the filler-binders because they often make up the majority of the tablet weight and volume. However, this fact is still not fully appreciated by pharmaceutical formulators and production personnel. A list of factors involved in the choice of a filter-binder can be found in Table 2.

Most all of the classic tablet fillers have been modified in one way or another to provide fluidity and compressibility. In viewing the scanning electron photomicrographs of the various direct-compression filler-binders, one is taken with the fact that none of the products consist of individual crystals. Instead, all of them are actually minigranulations or agglomerations that have been formed in the manufacturing process by means of co-crystallization, spray drying, etc. The resulting material thus is able to deform plastically in much the same manner as the larger particle size granules formed during the traditional wet granulation process. The key to making any excipient or drug directly compressible thus becomes obvious and the possibility of making all tablets by direct compression appears to be within the scope of present technology.

B. Soluble Filler-Binders

Lactose

Spray-dried lactose is the earliest and still one of the most widely used direct-compression fillers. It is one of the few such excipients available from more than a single supplier. In spite of many early problems, this material revolutionized tableting technology.

Coarse and regular grade sieved crystalline fractions of α-lactose monohydrate have very good flow properties but lack compressibility. However spray drying produces an agglomerated product that is more fluid and compressible than regular lactose [1].

In the production of spray-dried lactose, lactose is first placed in an aqueous solution which is treated to remove impurities. Partial crystallization is then allowed to occur before spray-drying the slurry. As a result the final product contains a mixture of large α-monohydrate crystals and spherical aggregates of smaller crystals held together by glass or amorphous material. The fluidity of spray-dried lactose results from the large particle size and intermixing of spherical aggregates. The compressibility is due to the nature of the aggregates and the percentage of amorphous material present and the resulting plastic flow, which occurs under compaction pressure.

The problem of compressibility of spray-dried lactose is still real and troublesome. The compressibility of spray-dried lactose is borderline, and furthermore, it has relatively poor dilution potential. Spray-dried lactose is an effective direct-compression filler when it makes up the major portion of the tablet (more than 80%), but it is not effective in diluting high-dose drugs whose crystalline nature is, in and of itself, not compressible. Furthermore, spray-dried lactose does not lend itself to reworking because of reduced compressibility upon initial compaction.

Spray-dried lactose has excellent fluidity, among the best for all direct-compression fillers. It contains approximately 5% moisture, but most of this consists of water of hydration. The free surface moisture is less than

Another form of cellulose advocated for direct compression is microfine cellulose, (Elcema). This material is a mechanically produced cellulose powder which also comes in a granular grade (G-250), which is the only form that possesses sufficient fluidity to be used in direct compression. Microfine cellulose is a compressible, self-disintegrating, antiadherent form of cellulose that can be made into hard compacts. However, unlike microcrystalline cellulose, it possesses poor dilution potential, losing its compressibility rapidly in the presence of noncompressible drugs. It is not a particularly effective dry binder due to the large particle size of the G-250 granules and the resistance to fracture under compression. Microfine cellulose forms few fresh or clean surfaces during compression because of the lack of slip planes and dislocations in the cellulose granules. Thus little interparticulate binding occurs, and sufaces "contaminated" by lubricant during mixing show little inclination to form firm compacts.

Inorganic Calcium Salts

The most widely used inorganic direct-compression filler is unmilled dicalcium phosphate, which consists of free-flowing aggregates of small microcrystals that shatter upon compaction. This material is available in a tableting grade under the names Emcompress or DiTab. Dicalcium phosphate is relatively inexpensive and possesses a high degree of physical and chemical stability. It is nonhygroscopic at a relative humidity of up to 80%. Dicalcium phosphate in its directly compressible form exists as a dihydrate. Although this hydrate is stable at room and body temperature, it will begin to lose small amounts of moisture when exposed to temperatures of 40 to 60°C [31]. This loss is more likely to occur in a humid environment than a dry environment. This anomaly is theorized to occur because at low humidities and high temperatures, the outer surfaces of the particles lose water of hydration and become case-hardened, preventing further loss. In a humid environment the loss continues to occur. When combined with a highly hygroscopic filler like microcrystalline cellulose, the loss of moisture may be sufficient to cause a softening of the tablet matrix due to weakening of the interparticulate bonds and to accelerate decomposition of moisture-sensitive drugs like vitamin A.

The fluidity of dicalcium phosphate is good, and glidants are generally not necessary. While it is not as compressible as microcrystalline cellulose and some sugars (Fast-Flo lactose, Emdex), it is more compressible than spray-dried lactose and compressible starch. It apparently deforms by brittle fracture when compressed, forming clean bonding surfaces. Lubricants exert little softening effect on compacts.

Because it is relatively water-insoluble, tablets containing 50% or more of dicalcium phosphate disintegrate rapidly. Dicalcium phosphate does dissolve in an acidic medium, but it is practically insoluble in a neutral or alkaline medium. Therefore, it is not recommended for use in high concentrations in combination with drugs of low water solubility. This is of particular concern in formulating tablets that may be used in geriatric patients where the incidence of achlorhydria is significant.

Dicalcium phosphate dihydrate is slightly alkaline with a pH of 7.0 to 7.4, which precludes its use with active ingredients that are sensitive to even minimal amounts of alkalinity. Tricalcium phosphate (TriTab) is less compressible and less soluble than dicalcium phosphate but contains a higher ratio of calcium ions [32]. Calcium sulfate, dihydrate N.F., is available in direct-compression forms [Delaflo, Compactrol].